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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,553	COURT ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03, 10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 12/5/2005, in which claims 14-21 were canceled, and claims 22-23 were newly added.

Election/Restrictions

Applicant's election of Group I (claims 1-13) in the reply filed on 12/5/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-13 and 22-23 read on the elected invention of Group I and are under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, International Application No. PCT/US01/25507 and Provisional Application Nos. 60/225,164 and 60/271,632, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior-filed application numbers do not provide literal or inherent support for the claimed method steps of claims 1-13 and 22. While the prior-filed applications suggest that the disclosed method of homologous recombination may be used to construct complex conditional targeting vectors, the specifications do not set forth the claimed method steps. For example, the prior-filed applications do not provide adequate written description for the method step of using homologous recombination to insert a nucleic acid encoding a selectable marker flanked by a pair of second recombining sites and a first recombining site into a second site into the gene in a bacterial artificial chromosome. The prior-filed applications do not teach how to use the disclosed recombination system to make a vector for the conditional knockout of a gene, where two first recombining sites remain in a gene and recombination of the two first sites produces a nucleic acid sequence that cannot be transcribed to produce a functional protein.

Claims 1-13 and 22-23 have an effective filing date of 2/12/2003.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 10/23/2003 and 10/1/2004, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

Specification

The disclosure is objected to because of the following informalities: the deposit numbers have not been provided for the deposited nucleotide cassettes (see page 44).

Appropriate correction is required.

Drawings

The drawings are objected to because the text within the shaded boxes of Figure 8 is illegible and will not reproduce well. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 4 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002; see the entire reference).

Regarding claim 1, Casanova et al teach a method for generating a vector for conditional knockout of a gene, comprising the following steps: (i) co-electroporating a BAC construct and a kanamycin cassette flanked by two LoxP sites (LoxP-Kan-LoxP) into *E. coli* JC8679 competent cells, (ii) selecting for kanamycin resistant clones, (iii) transforming the BAC DNA, from a bacterial colony that had undergone homologous recombination, into Cre-expressing bacteria to excise the nucleic acid encoding the selectable marker, which leaves a single LoxP site in the gene (iv) co-electroporating into *E. coli* JC8679 competent cells the BAC DNA comprising the single LoxP site and a plasmid comprising a FRT-PGK$_{Tn5}$neo-FRT-loxP flanked by two homology arms, and (v) transforming the resulting recombinant BAC into FLP-expressing bacteria to excise the marker gene (e.g. page 158, left column, 2nd full paragraph; page 158, paragraph bridging columns; Figure 1). Casanova et al teach the use of ET-cloning (homologous recombination in *E. coli* to insert the nucleic acid molecules encoding a selectable marker into the BAC construct (e.g. Figure 1). Casanova et al teach that the recombination of the remaining

two first recombining sites will produce a nucleic acid sequence that cannot be transcribed to produce a functional protein (e.g. page 158, left column, 2nd paragraph).

Regarding claims 3 and 4, Casanova et al teach the abovementioned method, where the first recombining sites comprise a LoxP site, and the second recombining sites comprise a FRT site.

Regarding claim 13, Casanova et al teach the use of markers that confer resistance of the cell to an antibiotic such as kanamycin (e.g. Figure 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12, 13, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002; see

the entire reference) in view of Lee et al (Genomics, Vol. 73, pages 56-65, 2001; see the entire reference) as evidenced by Buchholz et al (Nucleic Acids Research, Vol. 24, pages 3118-3119, 1996; see the entire reference).

The teachings of Casanova et al are described above and applied as before. Further, Casanova et al teach the use of Cre-expressing and Flp-expressing bacteria as taught by Bucholz et al (1996).

Bucholz et al is cited merely to provide evidence that the Cre-expressing bacteria used by Casanova et al comprise an inducible pL promoter operably linked to a nucleic acid encoding the Cre recombinase (e.g. page 3118).

Casanova et al do not teach homologous recombination wherein the cell comprises the pL promoter operably linked to a nuclei acid encoding Beta, Exo and Gam and wherein the first recombination site is FRT and the second recombination site is LoxP. Further, Casanova et al do not teach the use of Flpe recombinase encoded by a nucleic acid comprising an inducible promoter operably linked to a nucleic acid encoding the recombinase.

Lee et al teach a PL operon encoding beta, exo and gam under the control of the temperature-sensitive λ repressor (allele cI857) for use in BAC engineering (e.g. page 56, right column, 1st full paragraph; page 57, left column, 1st full paragraph). Further, Lee et al teach the use of the recombination system in combination with the flpe gene under the control of the P_{BAD} inducible promoter (e.g. strain EL250; Table 1). Lee et al teach that the recombination system is highly efficient and can produce recombination frequencies that are at least 50- to 100-fold higher than those obtained with plasmid based systems (e.g. page 64, left column, last paragraph). Lee et al teach the recombination of an FRT-kan-FRT cassette into the mouse *Eno2*

gene within a BAC vector (e.g. page 57, *Construction of plasmids*; Figure 1). Lee et al teach that the use of flpe provides a higher recombination frequency than the original flp gene (e.g. page 60, left column, 1st paragraph). With regard to the use of the recombination system for the construction of conditional targeting vectors, Lee et al state the following:

> This recombination system also facilitates the generation of complicated conditional targeting vectors. While the generation of such vectors often used to take several months, it can now be performed in only a few weeks. The ability to express reversibly Cre or Flpe recombinases in *E. coli* speeds this process even further. A selectable marker flanked with *loxP* of *FRT* sites can now be introduced into an intron of a gene and then be removed by transient Cre of Flpe expression, leaving behind a solo *loxP* or *FRT* site in the intron. See page 64, right column, 2nd paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method for generating a vector for conditional knockout of a gene of Casanova et al to include the phage lambda recombination system and inducible flpe expression taught by Lee et al because Casanova et al and Lee et al teach it is within the ordinary skill in the art to use homologous recombination in *E. coli* to engineer BAC vectors to produce conditional targeting constructs. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method to use FRT sites as the first recombination site and LoxP as the second recombination site because Casanova et al teach it is within the ordinary skill in the art to use of a LoxP-Kan-LoxP cassette to insert a single LoxP site and Lee et al teach it is within the ordinary skill of the art to use a FRT-Kan-FRT cassette to insert an FRT site into the intron of a gene. Further, Lee et al teach that the LoxP and FRT sites can be used interchangeably.

One would have been motivated to make such a modification in order to receive the expected benefit of increased efficiency of homologous recombination and FRT site-specific

recombination, which would decrease the amount of time required to make the targeting construct, as taught by Lee et al. Further, one would have been motivated to use FRT in place of LoxP and LoxP in place of FRT to have more options in the vector design and subsequent knockout of the gene by expressing cre or flpe in a targeted mouse, for example. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6-8, 10-13, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casanova et al (Genesis, Vol. 32, No. 2, pages 158-160, Published Online 2/13/2002; see the entire reference) in view of Stewart et al (US Patent No. 6,355,412; see the entire reference) as evidenced by Buchholz et al (Nucleic Acids Research, Vol. 24, pages 3118-3119, 1996; see the entire reference).

The teachings of Casanova et al are described above and applied as before. Further, Casanova et al teach the use of Cre-expressing and Flp-expressing bacteria as taught by Bucholz et al (1996).

Bucholz et al is cited merely to provide evidence that the Cre-expressing bacteria used by Casanova et al comprise an inducible pL promoter operably linked to a nucleic acid encoding the Cre recombinase (e.g. page 3118).

Casanova et al do not teach homologous recombination wherein the cell comprises the pL promoter operably linked to a nuclei acid encoding Beta, Exo and Gam and wherein the cell is a eukaryotic cell.

Stewart et al teach a method of performing homologous recombination in a host cell, comprising introducing a nucleic acid sequence encoding RecE/T or Redα/β recombinase (i.e. Lambda Exo and Beta) into a host cell, introducing a polynucleotide comprising a nucleotide sequence homologous to the nucleotide sequence of interest into the host cell, activating the expression of RecE/T, and selecting a cell from the population in which homologous recombination has occurred (e.g. column 28, lines 10-50; column 29, lines 9-35; column 28, line 51 to column 29, line 8; columns 25-27; paragraph bridging columns 37-38). Further, Stewart et al teach the use of Gam in addition to Exo and Beta or RecE/T (e.g. column 25, lines 5-28; Example 1). Stewart et al teach that a variety of host-vector systems may be utilized to introduce and express the protein-coding sequence of RecE/T or Redα/β, including prokaryotic and eukaryotic cells such as bacterial, yeast, plant, rodent, mice, human, insect or mammalian cells (e.g. column 28, lines 10-40). With respect to regulatory controls, Stewart et al teach that a range of different expression levels and a variety of regulatory sequences are known in the art and the ability to generate a wide range of expression is advantageous for utilizing the method (e.g. column 25, lines 5-44; column 24, line 50 to column 25, line 3). Stewart et al teach that the expression can be regulated by the P_L promoter of phage λ and the inducible lambda repressor CI_{857} (e.g. column 26, lines 1-27). Stewart et al teach that the nucleotide sequence of interest may be extrachromosomal and located on a bacterial artificial chromosome (e.g. column 20, lines 37-57; paragraph bridging columns 28-29). Moreover, Stewart et al teach that the lambda recombinases can be used to achieve high-efficiency targeted cloning (e.g. column 11, lines 3-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method for generating a vector for conditional knockout of a gene of Casanova et al to include the lambda beta, exo and gam genes operably linked to the pL promoter as taught by Stewart et al because Casanova et al and Stewart et al teach it is within the ordinary skill in the art to use homologous recombination to modify BAC constructs in a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to conduct high efficiency recombination in a variety of host cell types as taught by Stewart et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR, http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC)

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Jennifer Dunston
Examiner
Art Unit 1636

jad

JAMES KETTER
PRIMARY EXAMINER